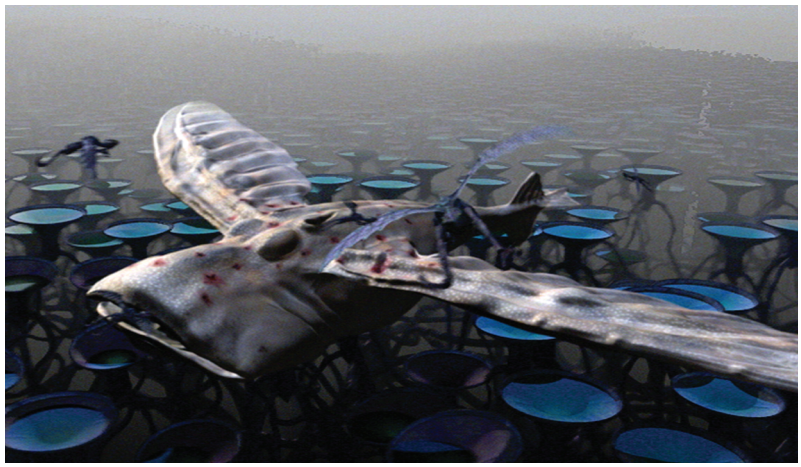

Alien death: A 'skywhale' has been hunted down over a pagoda forest on Blue Moon. (Image: Big Wave Productions.)

paleontology and molecular genetics.

But convergent evolution is only one side of a long-standing debate and there are many valid arguments against it. Incidentally, one of the most prominent proponents of convergence is Simon Conway Morris, who played one of the central parts on the science panel in *Alien Worlds*. The opposing view — that life, as we know it, looks and works the way it does because of the results of chance and historical contingency — is not reflected in the programme. It would have been interesting to see what *Alien Worlds* would have looked like with Conway Morris' key opponent, the late Stephen Jay Gould, as a scientific adviser.

Alien Worlds makes little mention of how life started on Aurelia or the Blue Moon, other than it will be carbon based. But obviously, the view of convergent evolution is based on observations on earthly life forms, which all originated from the same starting point and use essentially the same genetic systems. When starting with a radically different make-up, life may look radically different after all. In the programme, virtually no mention is made of how alien genetic systems might look, or what kinds of cells they might have. This is quite surprising, as otherwise in public science programmes genes and molecules are all the rage. Notably, there also seems to be hardly any sex in alien worlds.

As the role of contingency on historical starting conditions and the resulting constraints is hardly addressed, the viewer is left with the message that convergence prevails. No matter what the circumstances are, life will look similar at least in the sense that similar design features are used, just in different combinations; hence, for instance, the critters that are a bit like a bat, a bit like a bird and a bit like a bee.

If life comes up with the same solutions over and over again, this perhaps means that life on Earth may already have explored all possible solutions and that therefore all the features of aliens can be found somewhere on Earth. They may be less conspicuous or occur in a different context, but all of the aliens portrayed in *Alien Worlds* have features of earthly creatures. In that way, they are rather unenigmatic and, in the end, stranger and more alien life forms can be discovered in the natural history programmes that are shelved next to *Alien Worlds*. Artistically and because of the underlying conceptual framework of convergent evolution, the aliens are hardly stranger or more stunning than their earthly counterparts, which in turn have the great advantage of actually existing. For the time being, the Blue Planet is still stranger and more exciting than the Blue Moon.

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Shared architecture of bacteriophage SPO1 and herpesvirus capsids

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Viruses have probably existed for as long as cells. Recent structural studies of viral capsids have revealed similarities that span the domains of life and point to distant evolutionary connections between viruses that pre-date the division of their host organisms into domains [1–3]. Comparisons of adenovirus and phage PRD1 demonstrate this emerging theme: these viruses share a unique T=25 capsid geometry with unusual 'trimeric hexons' and a common core fold for the major capsid proteins [4]. We describe a novel structural link between herpesviruses and the bacteriophage SPO1 revealed by cryo-electron microscopy (cryoEM) data showing that the SPO1 capsid has icosahedral geometry with triangulation number T=16, a value previously associated uniquely with herpesviruses, as well as an asymmetric capsid surface molecule reminiscent of the 'triplex' molecule of HSV-1. We propose that the similarities go deeper, to a common capsid protein core fold of the phage HK97 class [5]. The shared architecture suggests a common ancestor for herpesviruses and phage SPO1 and supports a distinct lineage for herpesviruses and the tailed phages.

Herpesviruses have bacteriophage-like qualities reminiscent of dsDNA phages such as T4 [6]. These include procapsid assembly around a scaffold, post-assembly

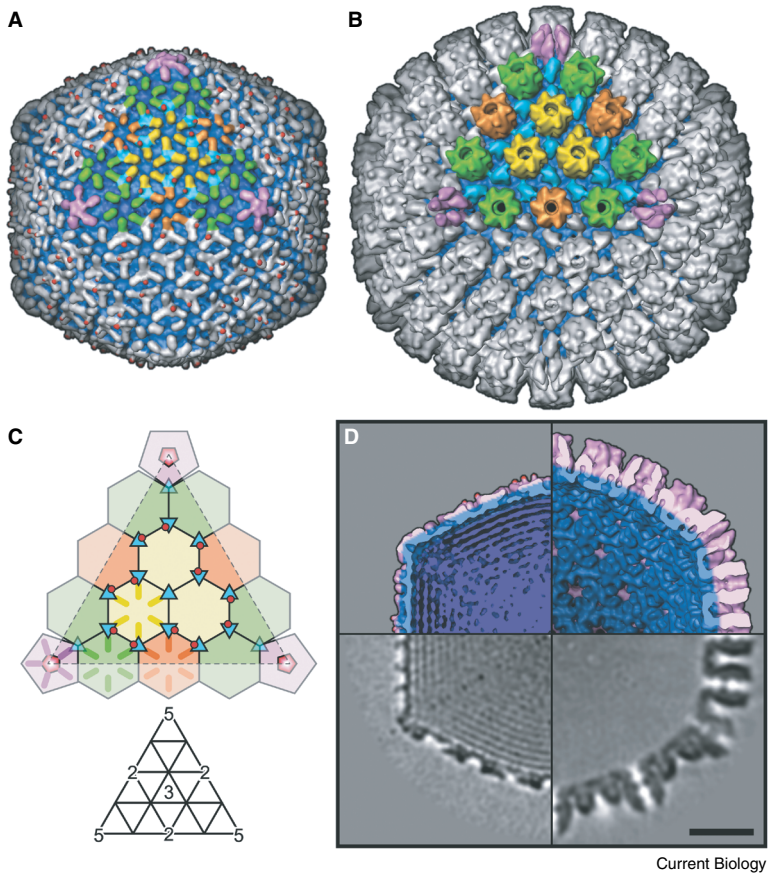

Figure 1. Capsid structure of phage SPO1 calculated to 20 Å resolution.

(A) Surface views along the icosahedral twofold axis of (A) the SPO1 capsid, and (B) the HSV-1 capsid. The capsids have been colorized as follows: the continuous capsid layer is dark blue; pentamer extensions are purple; hexon extensions are green, orange or yellow according to their quasi-equivalent positions; and additional density at sites of local three-fold symmetry are light blue. For SPO1, small spikes (red) extend from this trivalent density at an off-axis location. (C) Schematic representations of the subunit positions for SPO1 (top) and an outline of the quasi-equivalent sub-triangles of an icosahedral facet according to lattice geometry with triangulation number T=16 (bottom). (D) Sectioned views of the SPO1 (left) and HSV-1 (right) capsids, as surfaces (top) where the continuous floor layer is colored blue and the extended domains are pink, and as grey-scale encoded density (bottom). HSV-1 data courtesy of A.C. Steven and B.L. Trus, NIH. Bar = 200 Å.

proteolysis of the scaffold and major capsid proteins, maturation of the procapsid to a particle packed densely with DNA, binding of surface proteins to the exterior of the capsid, and a specialized vertex with associated proteins for DNA packaging. Recent data allow a more extensive characterization of the morphological similarities, including cryoEM structures on herpesviruses from more primitive species, such as channel catfish and oyster [7], and the description here of a bacteriophage whose capsid bears a strong resemblance to those of herpesviruses.

Electron microscopy studies by Eiserling and co-workers [8] revealed the overall organization of phage SPO1's icosahedral capsid, including an average diameter of 870 Å enclosing the dsDNA genome of ~140 kbp, and suggested that the likely triangulation number is T=16, i.e., pentamers at the icosahedral vertices and 150 hexamers on the facets according to classical quasi-equivalence [9]. This capsid geometry has been associated uniquely with herpesviruses and its observation in a bacteriophage would strengthen the argument for an evolutionary connection. To investigate further we have analyzed the SPO1 capsid by cryoEM (see Supplemental Data for details).

Three-dimensional reconstruction of the SPO1 capsid, calculated to 20 Å resolution, clearly establishes the triangulation number to be T=16 (Figure 1). The exterior surface is composed of a continuous floor level on top of which form 30 Å high oblong ridges in groups around sites of local quasi-sixfold symmetry and fivefold icosahedral vertices. The hexameric groups are arrayed around a cavity, whereas pentamer sites are occupied by a plug of additional density, but the similarity in shape between the hexamer and pentamer ridges suggests that their subunits are the same or have similar folds. The distal ends of the oblong ridges merge at most sites of local threefold symmetry into a lump of density that is slightly lower in profile, rising about 25 Å above the floor. These lumps are notably absent at the threefold sites adjacent to the pentamers, indicating that they are not extensions of the ridges but are a separate molecule. We note that a reconstruction of helical polyheads produced by an SPO1 mutant and lacking minor capsid proteins showed hexameric arrangements of oblong subunits remarkably similar to those in the current capsid reconstruction and similarly lacking the extra density at the local threefold sites (see Figure 6 of [8]). In the capsid reconstruction, a small spike extends outwardly a further 20 Å from this molecule starting at a point to one side of the local threefold axis and thus disobeying the local symmetry. Since this spike density is as strong as that of the rest of the capsid, we conclude that the spike is not randomly located in any of the three locally equivalent positions, but obeys global icosahedral symmetry. Further, this asymmetric molecule is reasonably assigned as a trimer, analogous to the trimeric capsid-stabilizing proteins of phages λ (gpD) and T4 (soc) but more closely resembling the heterotrimeric triplex molecule of herpesvirus [10]. Thus, trimer asymmetry correlates with T=16 capsid geometry in the structures

resolved to date. With only the examples of herpesvirus and SPO1, however, it is not yet clear whether the asymmetric trimer is somehow required to achieve T=16 geometry, or whether it is only a consequence of this geometry. In addition, until we isolate SPO1 procapsids, we cannot know whether the SPO1 trimer maintains procapsid stability, as in herpesvirus [11], or acts later, as in phages λ and T4.

No spike is evident for the molecule at the icosahedral threefold axis. Presumably, the enforced icosahedral symmetry renders the asymmetric portion of this molecule below the density used to contour the surface. We also note that the HSV-1 triplexes in the trivalent sites adjacent to the penton, as well as the next proximal-most set, are the least strongly bound and may be removed along with pentons by 2M GuHCl extraction [10], suggesting that they contribute least to stability in the mature capsid and that their binding strength diminishes with curvature of the capsid floor. By analogy, we suppose that curvature of the SPO1 capsid near the pentons disturbs the precise structural arrangement of the trivalent sites necessary to bind the capsid surface molecule, or weakens the binding sufficiently that the molecule is lost from these positions during sample preparation.

The maximum outer capsid diameter, vertex-to-vertex, is 1080 Å, smaller than the 1250 Å of HSV-1 and nearer that of the oyster herpesvirus at 1160 Å [7]. The major capsid proteins of these two herpesviruses vary from 150 kDa for HSV-1 to 120 kDa for oyster herpes, which correlates with the reduced size of the upper domain for the latter and hence the lower capsid diameter. We speculate that the lower domain is sufficient for maintaining the integrity of the assembled herpesvirus capsid and might be similar to the smaller 46 kDa SPO1 mature capsid protein in size and organization.

Evidence for common ancestry between the tailed phages and the herpesviruses, or at least between the genes responsible for assembly and structure of their capsids, has been building for several years, based on similarities of virion structure and composition and on mechanisms of virion assembly (see above). Very recently it has been suggested that the lower domain of the HSV-1 capsid protein shares the same polypeptide fold with the capsid subunit of phage HK97 [6,12], a fold that is also shared by other tailed phages, including T4, phi29 and P22 [13]. However, the herpesvirus major capsid protein has so far yielded only partially to crystallographic analysis (in particular a fragment of the upper domain [14]), thus precluding a comparison of folds. Here we extend this picture by showing that a phage and herpesvirus share the same detailed capsid architecture, including the T=16 subunit arrangement and the unusual heterotrimeric triplexes. We believe these observations, taken together, make a compelling case for common ancestry of the herpesviruses and the tailed phages and provide a new window on understanding the evolutionary history of viruses.

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Supplemental Data
Supplemental data including experimental procedures are available at http://www.current-biology.com/cgi/content/full/16/1/R11/DC1/

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